

Fiksna kombinacija perindoprila i amlodipina — optimalno liječenje arterijske hipertenzije i koronarne bolesti srca

Fixed combination perindopril-amlodipine — optimised treatment in hypertension and coronary artery disease

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SAŽETAK: Arterijska hipertenzija (AH) predstavlja najveći pojedinačni čimbenik rizika koji doprinosi globalnoj smrtnosti. Usprkos stalnom poboljšanju liječenja, samo jedna trećina liječenih bolesnika postiže ciljane vrijednosti arterijskog tlaka (AT). Novija klinička istraživanja navode da pristup korištenja monoterapije za kontrolu AH vjerojatno neće biti uspješan kod mnogih bolesnika. Stoga prednost ima kombinirana terapija, temeljem činjenice da AH doprinosi višestruki čimbenici, a postizanje kontrole AT sa samo jednim lijekom koje djeluje preko jednog mehanizma vjerojatno neće biti dostatno. Kombiniranjem lijekova u odgovarajućoj dozi smanjuje se doza pojedinačnih komponenti i učestalost nuspojava te se poboljšava suradljivost bolesnika. Temeljem dokaza iz studije Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure-Lowering Arm (ASCOT-BPLA) kombinacija inhibitora angiotenzin konvertirajućeg enzima (ACE) i blokatora kalcijevih kanala (CCB) predstavlja liječenje izbora kod AH. Kombinacija perindoprila i amlodipina jedini je oblik liječenja kombinacijom ACE inhibitora i CCB koje je dokazalo da zadovoljava primarni cilj antihipertenzivne terapije, tj. ukupno smanjenje pobola i smrti povezanog s AH. Krka je trenutno jedina generička tvrtka koja nudi fiksnu kombinaciju perindoprila i amlodipina i tako omogućava učinkovito liječenje prilagođeno pojedinačnim potrebama bolesnika i liječnika.

KLJUČNE RIJEČI: arterijska hipertenzija, fiksne kombinacije, arterijski tlak, perindopril, amlodipin.

SUMMARY: Hypertension is currently the biggest single risk factor contributing to global death. Despite the constantly improving treatments, only one third of patients who are treated have a normalisation of blood pressure (BP). Recent clinical trials suggest that the approach of using monotherapy for the control of hypertension is not likely to be successful in most patients. Combination therapy is preferred, based on the fact that multiple factors contribute to hypertension and achieving control of BP with a single agent acting through one particular mechanism may not be possible. Combining the medicines makes them available in a convenient dosing format and lowers the dose of individual components, thus reducing the side effects and improving compliance. Based on evidence from the Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure-Lowering Arm (ASCOT-BPLA), the combination of an angiotensin-converting enzyme (ACE) inhibitor with a calcium channel blocker (CCB) is one of the preferred therapeutic options. The combination perindopril-amlodipine is the only treatment among ACE inhibitor and CCB combinations that has been demonstrated to meet the primary objective of antihypertensive therapy, that is, overall reduction of hypertension-related death and morbidity. Krka is now the only generic company offering a fixed combination of perindopril and amlodipine and thus enabling effective treatment tailored to the individual needs of patients and physicians.

KEYWORDS: hypertension, fixed combinations, blood pressure, perindopril, amlodipine.

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Arterijska hipertenzija (AH) predstavlja vodeći čimbenik rizika prijevremene smrti i prema izvješću Svjetske zdravstvene organizacije iz 2010. godine, odgovorna je za 12.8% smrti i do 54% kardiovaskularnih bolesti diljem svijeta.¹ Paradoksalno je da usprkos ogromnom napretku liječenja antihipertenzivima broj osoba s nekontroliranom AH i dalje raste.² Oko 30% hipertenzivnih osoba nije svjesno svoga stanja i uopće nije podvrgnuto nikakvom liječenju. Od preostalih 70% koji su liječeni, samo 34% postiže preporučenu ciljnu vrijednost arterijskog tlaka (AT). Ovi podaci su zabrinjavajući uzevši u obzir dokazane dobrobiti smanjenja vrijednosti AT u obliku manje učestalosti infarkta miokarda (20-25%), zatajivanja srca (>50%) i moždanog udara (30-40%).³ Noviji podaci također ukazuju da neprimjerena kontrola AT je sam po sebi neovisan čimbenik rizika za razvoj dijabetesa kod hipertenzivnih pacijenata.⁴ Nedostaci u zbrinjavanju se općenito pripisuju nedovoljnom liječenju u smislu izbora lijeka ili doze, nepostojanja sinergije kada se daje više od jednog lijeka i problema sa suradljivošću bolesnika.³

Sadašnje smjernice za liječenje AH naglašavaju potrebu za poboljšavanjem dugoročnih kardiovaskularnih ishoda, kao i povećanjem broja bolesnika koji postižu ciljne vrijednosti AT.⁵ Dostupni podaci ukazuju da će najmanje 75% pacijenata obavezno trebati kombiniranu terapiju radi postizanja ciljnih vrijednosti AT.⁴ Sukladno spomenutom dopuna europskih smjernica o liječenju AH iz 2009. predlaže prilagođen individualni pristup kod liječenja AH posebice u visokorizičnih bolesnika. Rana intervencija i liječenje za snižavanje vrijednosti AT kombinacijom dva antihipertenziva preporuča se kod visokorizičnih pacijenata i onih s 2. stupnjem AH (tj. AT >20/10 mmHg iznad ciljnih vrijednosti) i ima za cilj smanjenja razvoja ili napredovanja oštećenja ciljnih organa prije nego što se dogodi kardiovaskularni događaj. Kada god je moguće, uporaba fiksne kombinacije bi trebala biti terapija izbora radi postizanja bržeg i većeg smanjenja vrijednosti AT i ograničenja broja lijekova te radi poboljšanja suradljivosti samog pacijenta.⁵ Općenito kombiniranje antihipertenzivnih lijekova iz komplementarnih klasa je približno pet puta učinkovitije u snižavanju vrijednosti AT nego povećanje doze jednog lijeka.⁴ U odnosu na slobodne kombinacije, fiksne kombinacije potiču bolju suradljivost u liječenju jer pojednostavljaju režim liječenja. Nadalje, pacijenti liječeni pojedinačnim antihipertenzivima koji se prebacuju na kombinaciju lijekova mogu postići značajne uštede troškova.⁵

Veliki broj fiksnih kombinacija dva lijeka je dostupan za kliničku upotrebu.⁶ Učinkovitost kombinacija antihipertenziva iz klase inhibitora angiotenzin konvertirajućeg enzima (ACE) i blokatora kalcijevih kanala (CCB) uz dodatni zaštitni učinak na srce i bubrege dobro je evidentirana. Posebice je dokazano da fiksna kombinacija perindopрила i amlodipina učinkovito smanjuje vrijednost AT i trenutno je to jedina kombinacija blokatora renin-angiotenzinskih sustava i CCB koja dokazano smanjuje ukupnu i kardiovaskularnu smrtnost, kao i velike kardiovaskularne događaje (**Tablica 1**). Stoga je ovo vrijedna opcija za liječenje AH kod visokorizičnih bolesnika.⁵ Kombinacijom perindopрила i amlodipina smanjuje se vrijednost povišenog AT putem dva komplementarna mehanizma koji djeluju sinergistički. Ovime se postiže učinkovitije smanjenje vrijednosti AT i bolja podnošljivost.³

Bolesnici sa stabilnom koronarnom bolesti srca (KBS) mogli bi imati koristi i od fiksne kombinacije perindopрила i amlodipina kojom se kombinira simptomatsko i prognostičko liječenje stabilne angine u jednoj tableti.³ Fiksna kombinacija perindopрила i amlodipina je prva fiksna kombinacija kod indikacije stabilne KBS. Prednosti terapije fiksnom kombinaci-

Hypertension is the leading risk factor for premature death, responsible for 12.8% of deaths worldwide, as well as up to 54% of cardiovascular deaths, according to a report from the World Health Organization published in 2010.¹ It is paradoxical that despite the enormous advances in antihypertensive therapy, the number of people with uncontrolled hypertension has continued to rise.² About 30% of hypertensive individuals are unaware of their condition and receive no treatment at all. Of the remaining 70% who do, only 34% achieve the recommended target blood pressure (BP). These data are of concern, considering the proven benefits of reducing BP, which translate into reduction in the incidence of myocardial infarction (20-25%), heart failure (>50%), and stroke (30-40%).³ Recent data also suggest that inadequate BP control is itself an independent risk factor for development of diabetes in hypertensive patients.⁴ The shortcomings in the management are generally attributed to insufficient treatment in terms of choice of the agent or dosage, absence of synergy when more than one agent is administered, and problems with compliance.³

Current guidelines for the management of hypertension emphasize the need to improve long-term cardiovascular outcomes, as well as to increase the proportion of patients achieving target BP.⁵ Available data suggest that at least 75% of patients will require combination therapy to achieve target BP.⁴ In this regard, the 2009 reappraisal of the European Guidelines on hypertension management recommends a more individually tailored approach in the management of hypertension, especially in high-risk patients. Early initiation and up-titration of BP-lowering treatment with a two-agent antihypertensive combination is recommended in high-risk patients to minimise the development or progression of target organ damage before a cardiovascular event occurs, and in patients with stage 2 hypertension (i.e. BP >20/10 mm Hg above BP goal). Whenever possible, use of a fixed combination should be favoured to attain a more rapid and greater BP reduction and to limit pill number in order to improve compliance.⁵ In general, combining antihypertensives from complementary classes is approximately 5 times more effective in lowering BP than increasing the dose of a single agent.⁴ Compared with free combinations, fixed combinations encourage better treatment compliance because they simplify the treatment regimen. Furthermore, converting patients treated with separate antihypertensives to a single combination product may produce substantial cost savings.⁵

A number of two-agent fixed combinations are available for clinical use.⁶ Strong evidence supports the antihypertensive efficacy of angiotensin-converting enzyme (ACE) inhibitor and calcium channel blocker (CCB) combinations with additional cardioprotective and renoprotective properties. In particular, evidence suggest that a fixed combination of perindopril and amlodipine effectively decreases BP and is currently the only renin-angiotensin system (RAS) inhibitor/CCB combination proven to decrease all-cause and cardiovascular mortality, as well as major cardiovascular events (**Table 1**). Therefore, is a valuable option for the management of hypertension, especially in high risk patients.⁵ The combination perindopril-amlodipine reduces hypertension via two complementary mechanisms of action working in synergy. This should lead to more efficient BP lowering and better tolerability.³

Patients with stable coronary artery disease (CAD) could also benefit from a fixed combination of perindopril and amlodipine, which combines the symptomatic and prognostic

Table 1. Summary of clinical benefits of the fixed combination perindopril-amlodipine in different clinical indications (Adapted from: Ferrari R. *Curr Med Res Opin.* 2008;24:3543-57.).

Hypertension	Effective BP reduction
	Two well-known agents with proven antihypertensive efficacy
	Combination used in the ASCOT trial
	Synergy of two complementary mechanisms of action
	24-h BP control
Coronary artery disease	Prognostic management of stable CAD (perindopril)
	Symptomatic management of stable angina pectoris (amlodipine)
	Aggressive BP reduction in stable angina pectoris
Type 2 diabetes	Reduction in the risk of new-onset diabetes
	Aggressive BP reduction in hypertensive diabetics
Reduction in secondary effects	Improved tolerability
	Reduction in peripheral edema due to amlodipine
Cardiovascular reduction	Reduction in cardiovascular morbidity and mortality
	Reduction in coronary heart disease and heart failure (perindopril)
	Reduction in the risk of stroke (amlodipine)
Pharmacoeconomics	Cost-effective in hypertension

jom antihipertenziva kao što su bolja podnošljivost, poboljšana suradljivost i sinergijski učinci te fibrinolitička funkcija također se primjenjuju i kod bolesnika s KBS.³

Konačno, učinkoviti rezultat snižavanja vrijednosti AT koji se očekuje za fiksnu kombinaciju perindopрила i amlodipina bi također trebao imati značajnu prednost kod dijabetičara s AH kod kojih je potrebno provesti agresivije liječenje.³

Krka je uvela svoj perindopril 2005. godine kao prvi generički perindopril dostupan na tržištima Srednje Europe. Godine 2007. uslijedila je fiksna kombinacija perindopрила i indapamida. Krkin perindopril i njegove kombinacije dostupne su u mnogim europskim državama i postaju najpropisivaniji generički perindopril u Europi.⁷ Godine 2011. Krka je pokazala da drži korak s najnovijim trendovima u liječenju AH te je uvela svoju fiksnu kombinaciju perindopрила i amlodipina, ponovno, kao prve i jedine generičke fiksne kombinacije ovih lijekova koja je dostupna u Europi. Uskoro će postati dostupan i hrvatskim liječnicima i bolesnicima pod zaštićenim imenom Dalneva. Ovaj lijek predstavlja jednu od najnovijih i najsnažnijih fiksnih kombinacija u Krkinom asortimanu antihipertenzivnih lijekova i namijenjen je pacijentima koji trebaju snažno, moderno, pouzdano i pojednostavljeno liječenje visokih vrijednosti AT primjenom lijeka koji nudi dodatnu zaštitu ciljnih organa i 24 satnu kontrolu AT. Krkina fiksna kombinacija perindopрила i amlodipina dostupna je u četiri različite doze (4 mg/5 mg, 8 mg/5 mg, 4 mg/10 mg, and 8mg/10 mg) što omogućuje liječnicima da odaberu najprikladniju kombinaciju doza za svakog pojedinog bolesnika. Time se može pomoći u liječenju AH i poboljšanju suradljivosti hrvatskih pacijenata.

management of stable angina into a single tablet.³ Fixed combination of perindopril and amlodipine is the first fixed combination in the indication of stable CAD. The advantages of fixed combination therapy, outlined above for hypertension, such as better tolerability, improved compliance and synergistic effects, such as fibrinolytic function, also apply in the CAD population.³

Finally, the efficient BP-lowering effect expected for a fixed combination of perindopril and amlodipine should also be of considerable advantage in diabetic hypertensive patients, who require aggressive management of their condition.³

Krka introduced its perindopril in 2005 as the first generic perindopril available on Central European markets. In 2007 followed the fixed combination of perindopril and indapamide. Krka's perindopril and its combinations are currently available in many European countries, and it has become the most prescribed generic perindopril in Europe.⁷ In 2011, Krka showed that it was following the newest trends in the treatment of hypertension and introduced its fixed combination of perindopril and amlodipine, again, as the first and only generic fixed combination of perindopril and amlodipine available in Europe. Soon it will be available to Croatian physicians and patients under the brand name Dalneva. It is one of the newest and most potent fixed combinations in Krka's range of antihypertensives and it is intended for patients, who need a powerful, modern, reliable and simplified treatment of high BP, with a medicine that provides additional protection of target organs, and 24-hour control. Krka's fixed combination of perindopril and amlodipine is available in four strengths (4 mg/5 mg, 8 mg/5 mg, 4 mg/10 mg, and 8 mg/10 mg), which allows the physician to choose the most appropriate strength for each patient. This might facilitate the management of hypertension and improve compliance among the Croatian patients.

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